Remarks

Claims 34 and 40 are pending in this application. Claims 39 and 51 are canceled in this amendment without prejudice to Applicants' rights to pursue the subject matter recited by them in one or more divisional, continuation, and/or continuation-in-part applications. No new matter has been added.

Applicants respectfully submit that claims 34 and 40 are allowable for at least the following reasons.

A. The Indefiniteness Rejection Should Be Withdrawn

On page 2 of the Office Action, claims 34 and 40 are rejected as allegedly indefinite. In particular, it is alleged that the claims' recitation of the "therapeutically effective amount of" 5 mg descarboethoxyloratadine ("DCL") is indefinite based on the assertion that such a recitation can encompass: 1) single effective dose of DCL; and 2) multiple effective doses but with a cumulative effect of 5 mg per day. (Office Action, page 2). Applicants respectfully traverse this rejection.

First, Applicants respectfully point out that the claims do not recite "5 mg," but instead recites "0.1 to 5 mg."[1] Second, Applicants respectfully point out that single and multiple doses are indeed contemplated. However, Applicants submit that the fact that both are contemplated does not render the claims indefinite.

As well-settled, the test for definiteness is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." (*See Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986)). Therefore, "the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles." (*Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366 (Fed. Cir. 2004)). In this regard, it is well-established that a claim is indefinite "[o]nly when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction." (*Id.*). Applicants respectfully submit that the pending claims clearly have a "meaning discernible to one of ordinary skill in the art," and their meaning is far from being "insolubly ambiguous." (*Id.*).

Claim 34 recites, in part, the administration of DCL in an amount from 0.1 to 5 mg per day. As such, it is clear that the claim contemplates the recited amount to be

[1] This issue is discussed in more detail herein elsewhere.

achieved in a day regardless of whether it is by single or multiple administrations. Indeed, the specification makes it clear that the recited dose may be achieved in "single or divided doses." (Specification, page 14, line 14). Thus, the meaning of claim 34 is clearly "discernible to one of ordinary skill in the art." (*Id.*).

It is further alleged in the Office Action that the claims are indefinite because it is unclear whether DCL is externally administered or *in situ* generated. (Office Action, page 2). In this regard, Applicants respectfully submit that the term "administration" refers only to the administration to a human of a substance as it exists outside the body. (*See Ex parte Barberich*, Appeal No. 2005-0906, submitted in Applicants' Response of January 9, 2006; also attached hereto for the Examiner's convenience as **Exhibit 1**).[2]

Indeed, the term "administration" is used in the specification in a manner that is completely consistent with that interpretation. For example, the specification describes dosage forms (*e.g.*, tablets and capsules) of DCL that can be used in methods of the invention. (*See, e.g.*, Specification, pages 16-17 and Examples 7-9). There, it is clearly disclosed that a fixed amount of active ingredient, *i.e.*, DCL, is used to prepare, for example, the tablets or capsules. The disclosure of dosage forms presupposes the existence of DCL prior to its administration to a patient. Furthermore, the specification discloses the *ex vivo* synthesis and preparation of DCL. (*See* specification, Example 1). It is apparent that DCL, synthesized and prepared using, for example, the methods disclosed in the specification, would exist outside the patient's body.

Furthermore, the file history clearly reflects that the term "administration" is intended to mean "external administration," as evidenced by Applicants' various remarks regarding unexpected results associated with a method of using DCL over a method of using loratadine. (*See, e.g.*, Applicants' Response of January 9, 2006, pages 19-20). Such remarks clearly evidence that the "*in situ* generation" of DCL by, for example, the administration of loratadine is not contemplated in this application.

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[2] Although issues regarding indefiniteness of the term "administration" were not present in *Ex parte Barberich*, it is clear that the Board considered that the term contemplates administration of a substance as it exists outside the body, as evidenced by its decision that the claims to "administration of a metabolite of ziprasidone" were not anticipated by prior disclosure of the administration of the parent compound ziprasidone.

For at least the foregoing reasons, Applicants respectfully submit that the pending claims are not indefinite, and thus, request that the rejection of the claims be withdrawn.

B. The Written Description Rejection Should Be Withdrawn

On pages 2-3 of the Office Action, claims 34 and 40 are rejected as allegedly failing to comply with the written description requirement. In particular, it is alleged that the phrase "adapted for administration in a single dose per day" and the "5 mg" dose are not supported by the specification. (Office Action, pages 2-3). Applicants respectfully traverse this rejection.

Applicants respectfully point out that claims 34 and 40 do not contain the phrase "adapted for administration in a single dose per day."[3] In addition, it is respectfully pointed out that claim 34 does not recite the administration of "5 mg" DCL.[4] Instead, claim 34 recites the administration of DCL in an amount "from 0.1 to 5 mg per day," which finds clear and express support in the specification (*See* specification, page 14, lines 15-16). Therefore, Applicants respectfully submit that claims 34 and 40 are adequately supported by the specification and claims as originally filed, and thus request the rejection of the claims be withdrawn.

C. The Enablement Rejection Should Be Withdrawn

On pages 3-4 of the Office Action, claims 48 and 70-71 are rejected as allegedly not enabled. In particular, it is alleged that the claims are not enabled based on the Examiner's assertion that the specification would be "considered guiding one skilled in the art to use multiple dosage units of the most preferred oral dose composition in units about 0.2 mg to about 1 mg to achieve the required daily dose range which should be about 0.1 mg to about 5 mg." (Office Action, page 3). It is further alleged that the specification does not provide "enablement for a single unit

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[3] Applicants also submit that even if the claims did contain such a phrase, the phrase is adequately supported by the specification and claims as originally filed. However, since the claims do not contain the phrase, it is unnecessary to address the support for that phrase.

[4] Applicants note that the canceled claims 39 and 51 recite "less than 5 mg" and "5 mg" of DCL, respectively. As Applicants believe that such doses are fully encompassed by claim 34, claims 39 and 51 are canceled without prejudice solely to expedite the prosecution of this application.

oral dosage form in 5 mg per unit dose with efficacy in maintaining serum concentration." (*Id.*, page 4). Applicants respectfully disagree with each of these allegations.

First, with regard to the allegation that the specification guides one skilled in the art to use "multiple dosage units of ... 0.2 mg to 1 mg [DCL] to achieve ... 0.1 mg to 5 mg [doses]," Applicants respectfully submit that such an allegation has no basis and is simply arbitrary. As discussed above, the specification discloses that:

> In general, the total daily dose range ... is from about 0.1 mg to less than about 10 mg administered in single or divided doses orally, topically, transdermally, or locally by inhalation. For example, a preferred oral daily dose range should be from about 0.1 mg to about 5 mg. A more preferred oral dose is about 0.2 mg to about 1 mg.

(Specification, page 14, lines 10-17) (emphasis added). Clearly, a reasonable interpretation would be that the disclosed amounts of DCL can be administered in "single or divided doses," but not that 0.2 mg to 1 mg unit dosages are administered multiple times to achieve 0.1 mg to 5 mg doses.[5]

Be that as it may, Applicants respectfully point out that the pending claims recite, in part, the administration of DCL in an amount from 0.1 to 5 mg per day. Therefore, although Applicants respectfully disagree with the Examiner's interpretation of the teachings of the specification for the reasons discussed above, it is respectfully pointed out that the Examiner's interpretation (*i.e.*, that the specification guides one skilled in the art to use multiple dosage units of the most preferred oral dose composition in units about 0.2 mg to about 1 mg to achieve the required daily dose range which should be about 0.1 mg to about 5 mg) would still enable claims 34 and 40, which recite 0.1 to 5 mg per day dose.

Further, with regard to the allegation that the specification does not enable "a single unit oral dosage form in 5 mg[6] per unit dose with efficacy in maintaining serum concentration," Applicants respectfully point out that no showing of "efficacy in

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[5] In addition, the Examiner's interpretation would not make sense because it would be unreasonable that one would attempt to achieve, for example, 0.1 mg dose by administering unit dosage forms containing, for example, 0.2 mg of DCL multiple times.

[6] Applicants remind the Examiner that the claims do not recite solely 5 mg.

maintaining serum concentration" is required for the description to be enabling for the claimed method. Nevertheless, Applicants submit herewith a copy of the package insert of Clarinex®, which post dates the priority of the instant filing date (attached hereto as **Exhibit 2**).[7] The insert shows that Clarinex® is a composition comprising 5 mg of DCL as an active ingredient, and that 5 mg DCL once a day is effective (*i.e.*, the recommended dose is 5 mg once a day). Therefore, in view of this additional evidence, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, ¶1 be withdrawn.

D. The Obviousness Rejection Should Be Withdrawn

On pages 4-6 of the Office Action, claims 34 and 40 are rejected as allegedly obvious over Atsushi *et al.*, *J. Clin. Ther. Med.*, 6(12): 2689 (1990) ("Atsushi") in view of Hilbert *et al.*, CA 108: 31237 (1988) ("Hilbert"), Garattini, *Clin. Pharm.*, 10: 216-227 (1985) ("Garattini"), and Clissold *et al.*, *Drugs*, 37: 42-57 (1989) ("Clissold"), or alternatively, over Shareeah, *Intl. Dermatology*, 31(5): 355-356 (1992) ("Shareeah"), in view of Hilbert, Garattini, and Clissold. In particular, it is alleged that the claims are obvious based on the allegation that Atsushi or Shareeah discloses the treatment of urticaria using 10 mg of loratadine and that Clissold discloses that 10 mg of loratadine is subjected to 50 % conversion into DCL.[8] (Office Action, pages 4-6). Applicants respectfully traverse this rejection.

1. No *prima facie* case of obviousness is established

Applicants respectfully submit that a *prima facie* case of obviousness has not been established by the references cited by the Examiner. This is in part because none of the references disclose or suggest the use of 0.1 to 5 mg of DCL for the treatment of urticaria. As the Examiner indicates, Atsushi and Shareeah disclose the treatment of urticaria using loratadine, but are silent regarding DCL. Although Clissold discloses that some portions of loratadine convert into DCL, it is also completely

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[7] The NDA holder of Clarinex® Schering-Plough is a licensee of the instant application.

[8] Although Hilbert and Grattani are cited for the rejection, they are not relied on in the substance of the rejection. Hilbert is an abstract directed to the pharmacokinetics of loratadine, and Grattani is a review article generally directed to pharmacokinetics of metabolites. These two references are not further addressed here.

silent with regard to the efficacy of DCL in treating any disorders, much less the specific disorder urticaria. Finally, none of the references alone or in combination suggest the method of using DCL for the treatment of urticaria in the claimed amount range.

Likewise, since none of the references disclose or suggest the claimed method, no reasonable expectation of success would have existed at the time of this invention. First, this is so since it was known at the time of this invention that not all antihistamines are effective in treating allergic rhinitis. In this regard, Applicants respectfully invite the Examiner's attention to *Remington's Pharmaceutical Sciences*, 18th Ed., pp. 1124-1125 (1990) ("Remington"), a copy of which is attached hereto as **Exhibit 3**. As the Examiner will see, Remington teaches that while "enormous number of clinical conditions for which antihistaminic drugs have been suggested" are known, these drugs "vary from ***effective*** to ***ineffective*** in these conditions." (Remington, page 1124 at last paragraph (emphasis in original)). Thus, Remington recognizes "the complex therapeutic problem that confronts the thoughtful physician in the selection of antihistamine." (*Id.*). Therefore, in view of the "complex therapeutic problem ... in the selection of antihistamine" due to the "enormous number of clinical conditions for which [antihistamines] have been suggested" and the varying degree of effectiveness of various antihistamines, it is clear that no reasonable expectation of successfully using any antihistamine for the treatment of any disorder would have existed. Significantly, there certainly was no reasonable expectation, in view of Remington, of success in using DCL for treating allergic rhinitis.

In addition, Applicants respectfully invite the Examiner's attention to Michel *et al.*, *Contact Dermatitis*, 36: 147-149 (1997), Parslew *et al.*, *Clin. Exp. Allergy*, 30: 1161-1165 (2000), and McClintock, *The New Zealand Medical Journal*, 108: 208 (1995), which are references of record and are also attached hereto as **Exhibits 4-6** for the Examiner's convenience. As the Examiner will see, each of these references discloses that some antihistamines actually cause skin reactions rather than treating them. Therefore, in view of the varied reactions to various antihistamines, those of ordinary skill in the art would not have had reasonable expectation of successfully

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14 Again, Applicants remind the Examiner that his cited art refers to physicians as the ordinary skilled artisan.

using DCL for the treatment of urticaria from the teachings of Atsushi/Shareah and Clissold. For these reasons alone, Applicants respectfully submit that the rejection of the claims should be withdrawn.

2. Any presumption of obviousness should be rebutted in view of the teaching away and unexpected results in the record

Even assuming, *arguendo*, a *prima facie* case of obviousness were established by the cited references, Applicants respectfully submit that sufficient teaching away and unexpected results are in the record to rebut any presumption of obviousness. It is well settled that even a *prima facie* obviousness can be rebutted by showing that the art in the whole teaches away from the claimed invention. (*See, e.g., Ex parte Baberich*, **Exhibit 1**, page 10). In this regard, Applicants respectfully point out that the art as a whole would have taught those skilled in the art away from the claimed method.

Applicants respectfully submit that those skilled in the art, at the time of this invention, would have been discouraged from using DCL for the treatment of urticaria. This is because it was known that antihistamines having structures or mechanisms of action, or both, similar to DCL are associated with various adverse effects, some of which are serious. Thus, in view of the concerns regarding the serious adverse effects which may well have been associated with the administration of DCL, those skilled in the art would not have contemplated to use DCL for a relatively minor disorder such as urticaria.[9] Thus, for this evidence alone, Applicants respectfully submit that any presumption of obviousness should be rebutted.

In addition, and perhaps more importantly, Applicants respectfully point out that the evidence in the record demonstrating that the claimed method has surprising or unexpected benefits must also be considered. Such evidence was presented, for example, in Examples 4 and 5 of the specification. This evidence alone is sufficient to rebut any *prima facie* case of obviousness. (*See In re May*, 547 F.2d at 1092-3; and *In re Chupp*, 816 F.2d at 646). Applicants further point out that evidence of

[9] There is abundance of evidence in the record in support. For example, Yap *et al.*, *Clin. Exp. Allergy*, 29(suppl): 15-24 (1999), *Goodman & Gilman's Pharmaceutical Basis of Therapeutics*, 9th Ed., 1607 (1996) and Storms Declaration, all of which were submitted with Applicants Response of January 9, 2006, show that the concerns existed with regard to the potential adverse effects of DCL.

unexpected benefit as disclosed in Example 4 is particularly relevant to the rejection based on Atsushi/Shareeah and Clissold for the following reasons.

Example 4 shows that DCL is 5 to 7 fold less potent in promoting tumor growth than loratadine. (Specification, Example 4). For further support, Applicants invite the Examiner's attention to the Tarantino Declaration, which was submitted with Applicants' Response of January 6, 2006. In his declaration, Dr. Tarantino concludes that he would have concluded, based on Applicants' data disclosed in Example 4, that DCL was a better drug candidate than loratadine because Example 4 shows that DCL is less immunotoxic than loratadine. (*See* Tarantino Declaration, ¶ 9-11). Furthermore, Dr. Tarantino, pointing to Brandes *et al.*, *Journal of National Cancer Institute*, 8(10): 770-775 (1994)[10], attests to the fact that the *in vitro* assay disclosed in Example 4 correlates well to the *in vivo* tumor promotion assay disclosed in Brandes. (*Id.*, paragraphs 12-17). Based on this, Dr. Tarantino states that it would have been reasonable to conclude, based upon the data disclosed in Example 4 and what was known about the assay at the time, that DCL is less potent in promoting tumor growth than loratadine. (*Id.*, paragraphs 16-17).

On the other hand, Clissold, while disclosing that some portion of loratadine converts into DCL once loratadine is administered, also teaches that some portion of loratadine still remains in the plasma hours after the administration. (*See Clissold*, Figure 3). Therefore, the administration of 10 mg loratadine as disclosed in Atsushi or Shareeah, where loratadine itself would remain in the plasma, cannot achieve the same beneficial effects achieved by the administration of, for example, 5 mg of DCL where no loratadine would be present in the plasma. In this regard, Applicants point out that the administration of 5 mg DCL is unexpectedly beneficial, especially over the method where loratadine itself is administered.

Therefore, considering those of ordinary skill in the art would have been discouraged from using DCL for the treatment of urticaria, and that the administration of DCL confers unexpected benefits as compared to the administration of loratadine, Applicants respectfully submit that any presumption of obviousness should be rebutted.

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[10] Brandes also teaches away in that it shows loratadine is a tumor promoter. Thus, any rejection based upon the use of loratadine must take this into consideration.

For these additional reasons, Applicants respectfully submit that the claims are not obvious over any combination cited by the Examiner, and thus respectfully request that the rejection be withdrawn.

Conclusion

Applicants respectfully submit that all of the pending claims are allowable, and request that rejections directed to the claims be withdrawn.

Should any issues remain, the Examiner is respectfully requested to telephone the undersigned.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date October 5, 2006

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